Potassium Iodide[1]

$$\boxed{\text{KI}}$$

[7681-11-0] · IK · Potassium Iodide · (MW 166.00)

(source of iodide ion for nucleophilic displacement reactions;[4-9] cleaves some ethers in the presence of acid;[10-12] acts as a mediator in electrochemical oxidations of aldehydes;[13] reacts with sulfonyl chlorides to give symmetrical thiosulfonic *S*-esters;[14] with oxidizing agents, iodinates aromatic compounds;[15] iodinates organothallium compounds[16])

Physical Data: mp 681 °C; bp 1330 °C; *d* 3.130 g cm^{-3}.

Solubility: very sol cold H_2O (127.5 g/100 mL, 6 °C), hot H_2O (208.0 g/100 mL, 100 °C); sol alcohol (1.88 g/100 mL, 25 °C), acetone (1.31 g/100 mL, 25 °C); slightly sol ether, ammonia.[2]

Form Supplied in: white solid (crystalline, granular, or powder); widely available. *Drying:* can be dried under vacuum over P_2O_5 at 70-100 °C.[3]

Handling, Storage, and Precautions: slightly deliquescent in moist air, and upon long exposure to air will turn yellow due to liberation of iodine; storage in a dry or inert atmosphere recommended.

Introduction.

KI is used primarily as a source of iodide in organic synthesis. KI can often be used interchangeably with NaI (see *Sodium Iodide* and *Tetra-n-butylammonium Iodide*).

Displacement Reactions.

KI will react with alkyl halides to give alkyl iodides. Alkyl iodides have been prepared from alkyl chlorides and bromides using KI supported on alumina.[4] The product iodide may be isolated or may react with a second nucleophile (e.g. *Dimethyl Sulfoxide*).[5] KI/*Phosphoric Acid* has been used to convert 1,6-hexanediol to 1,6-diiodohexane[6] and cyclohexene to cyclohexyl iodide.[7] KI reacts with aryl diazonium compounds to give aryl iodides.[8] This reaction has been shown to involve radicals, and proceeds faster and in higher yield in the absence of oxygen.[9]

Ether Cleavage Reactions.

KI in acetic acid or formic acid has been used to cleave aryl methyl ethers in high yield (yields were somewhat higher with KI than with NaI).[10] KI/H_3PO_4 has been used to convert THF to 1,4-diiodobutane.[11] KI/*Boron Trifluoride Etherate* cleaves methyl, allyl, and benzyl ethers and opens cyclic alkyl ethers (including THF and epoxides) to give iodo alcohols.[12] Aryl methyl ethers are cleaved slowly by this reagent, allowing for some selectivity.

Electrochemical Oxidations.

KI has been used as a catalytic mediator in the electrochemical oxidation of aldehydes to esters[13] and nitriles.[13c] (NaI and Et_4NI may be used in place of KI in these electrochemical oxidations.)

Preparation of Symmetrical Thiosulfonic *S*-Esters.

KI reacts with sulfonyl chlorides (RSO_2Cl) to give thiosulfonic *S*-esters (RSO_2SR).[14]

Iodination of Aromatic Hydrocarbons.

$KI/O_2/NO^+BF_4^-$ in TFA/CH_2Cl_2 or TFA iodinates aromatic hydrocarbons; however, the reaction fails with electron-deficient aromatics.[15] (NaI, n-Bu_4NI, and *Iodine* may be substituted for KI.) KI reacts with arylthallium bis(trifluoroacetate) compounds to give aryl iodides (and thallium triiodide) (eq 1).[16] Vinyl iodides have been prepared similarly from vinylthallium bis(trifluoroacetates).[16f]

$$(1)$$

80-84%
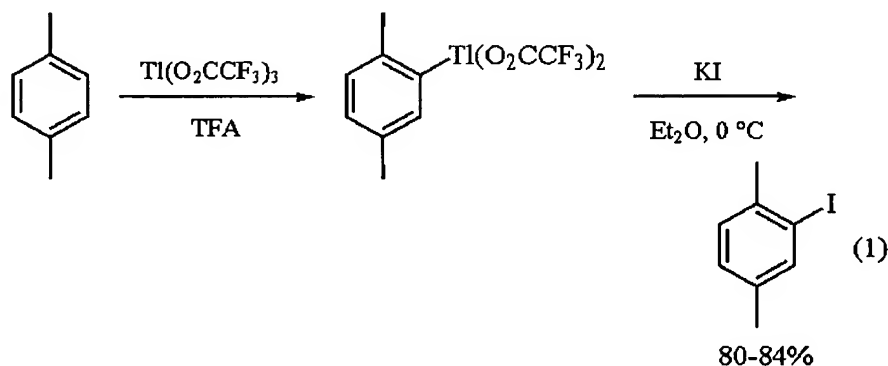
1. (a) *Kirk-Othmer Encyclopedia of Chemical Technology*, 3rd ed.; Wiley: New York, 1983; Vol. 18, p 939. (b) *Comprehensive Inorganic Chemistry*; Bailar, J. C.; Eméleus, H. J.; Nyholm, S. R.; Trotman-Dickenson, A. F., Eds.; Pergamon: Oxford, 1973; Vol. 1, pp 402-413.
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Chlorine[1]

$$Cl_2$$

[7782-50-5] · Cl_2 · Chlorine · (MW 70.91)

(powerful oxidizing and chlorinating agent)

Physical Data: yellowish-green gas, mp -101 °C, bp -34 °C; d 3.21 g cm^{-3} (gas, rt), 1.56 g cm^{-3} (liq, -35 °C).

Solubility: sl sol water (0.7 g in 100 mL at 20 °C); sol acetic acid, benzene, aliphatic hydrocarbons, chlorinated solvents, DMF.

Form Supplied in: packaged in cylinders with stainless steel or monel regulators.

Preparative Methods: chlorine is commercially available, but small quantities can be generated in the laboratory. The most common procedure involves the treatment of solid $KMnO_4$ with conc HCl (0.89 g of $KMnO_4$ and 5.6 mL of conc HCl per g of chlorine required).[2] It is recommended that chlorine so generated be dried by passing in succession through gas-washing bottles containing H_2O (to remove HCl), concd H_2SO_4 (to remove H_2O), and glass wool (to remove spray).[3] Preparations using conc HCl/MnO_2[4] or by heating $CuCl_2$ (anhyd)[5] have also been reported.

Analysis of Reagent Purity: iodometric titration; the chlorine can be volatilized and the moisture and residue determined gravimetrically.[1a]

Purification: commercial chlorine should be purified with H_2SO_4, CaO, and P_2O_5 and subsequently condensed in a dry ice-acetone bath and vaporized, repeatedly, while the noncondensable gases are removed with a pump.[4]

Handling, Storage, and Precautions: [5] highly toxic, nonflammable gas. Forms explosive mixtures with hydrogen, acetylene, or anhydrous ammonia. It is corrosive when moist. Chlorine is a strong oxidant and reacts violently with combustible substances, reducing agents, organic compounds, phosphorus, and metal powders. Avoid skin contact. Use protective clothing and a full-face respirator equipped with a NIOSH-approved organic vapor-acid gas canister. Cylinders should be stored away from sources of heat. All reactions should be conducted in a well-ventilated fume hood. The amount of chlorine added to a reaction mixture can be determined by weighing the cylinder before and after addition, or by condensing the required volume into a calibrated vessel and subsequently allowing it to volatilize while connected to the reaction vessel, or by generation from a known quantity of $KMnO_4$.

Substitution Chlorination.

Chlorine atoms, obtained from the dissociation of chlorine molecules by thermal or photochemical energy, react with saturated hydrocarbons by a radical chain mechanism. Chlorine reacts with methane to form methyl chloride, methylene chloride, chloroform, and carbon tetrachloride.[1a] Trialkylboranes have also been used to induce the radical chlorination of alkanes, e.g. chloro-2,3-dimethylbutanes are produced from 2,3-dimethylbutane.[6] Ethers are also chlorinated by photoinduced radical substitution reactions (eq 1).[7a]

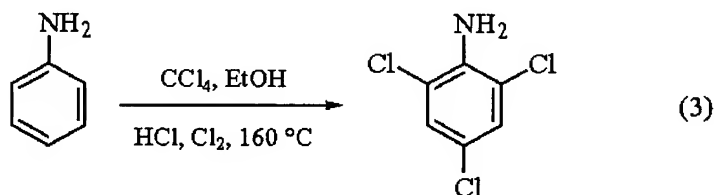$$Et_2O + Cl_2 \xrightarrow{h\nu} EtO\underset{}{\overset{Cl}{\bigwedge}} \quad (1)$$

The chlorination of carboxylic acids with molecular chlorine is catalyzed by phosphorus and its trihalides.[7b] Chlorine has been used to chlorinate methyl esters of carboxylic acids to form monochloro esters.[8] Chlorinations with chlorine favor the (o - 1)-position rather than the (o - 2)-position obtained with *Sulfuryl Chloride*.[8] Thus the chlorination of methyl heptanoate with chlorine results mainly in methyl 6-chloroheptanoate, whereas chlorination with sulfuryl chloride results mainly in methyl 5-chloroheptanoate.[8] Low temperatures are required for the chlorination of long-chain carboxylic acid methyl chlorides, as unsaturated compounds are formed at higher temperatures due to the elimination of HCl.

The main products of the chlorination of carbamates are the N-dichloro derivatives (eq 2).[7c]

$$H_2NCO_2R \xrightarrow{Cl_2 \text{ (aq)}} Cl_2NCO_2R \quad (2)$$
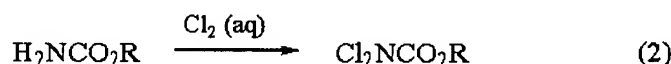
Aromatic amines react readily with chlorine, e.g. aniline is chlorinated to give 2,4,6-trichloroaniline in high yield (eq 3).[7d]

$$\underset{}{\overset{NH_2}{\bigcirc}} \xrightarrow[\text{HCl, Cl}_2, \text{ 160 °C}]{\text{CCl}_4, \text{ EtOH}} \underset{Cl}{\overset{NH_2}{\underset{}{\bigcirc}}} \quad (3)$$

Primary and secondary amides react with chlorine to give N-chloroamides and HCl.[7e] The reaction is reversible, and the products are favored by highly polar solvents.

α-Chlorination of aliphatic acids has been achieved with chlorine using enolizing agents like chlorosulfonic acid, H_2SO_4, HCl, or $FeCl_3$ with a radical trapper like m-dinitrobenzene, oxygen, or chloranil.[9] The imidyl hydrogen atoms of aldazines can be substituted with chlorine (eq 4).[7f]

$$(4)$$
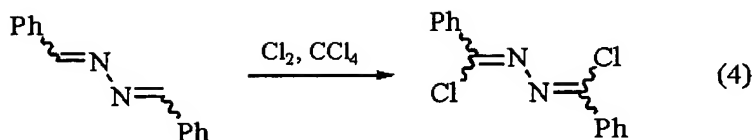
Addition Chlorination.

Saturated chlorides are formed when chlorine reacts with alkenes, e.g. chlorination of ethylene results in ethylene dichloride and chlorination of vinyl chloride gives 1,1,2-trichloroethane.[1a] These alkyl chlorides are important synthetic intermediates, e.g. 1,1,2-trichloroethane can be converted into vinylidene chloride in an alkaline medium.[1a] The addition of chlorine to 1-trimethylsilyl-1-alkenes in CH_2Cl_2 at low temperatures, followed by the elimination of Me_3SiX with methanolic sodium methoxide at 25 °C, produces vinyl chlorides in good yields (eq 5).[10]

$$(5)$$
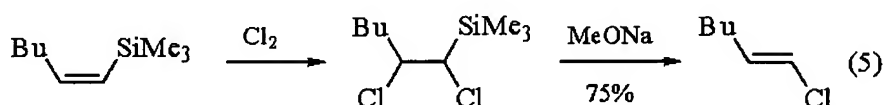
The radical chain addition reactions of chlorine are initiated by light or the walls of the reaction vessel and inhibited by oxygen. Some ionic addition reactions are accelerated by *Iron(III) Chloride, Aluminum Chloride, Antimony(V) Chloride*, or *Copper(II) Chloride*.[11]
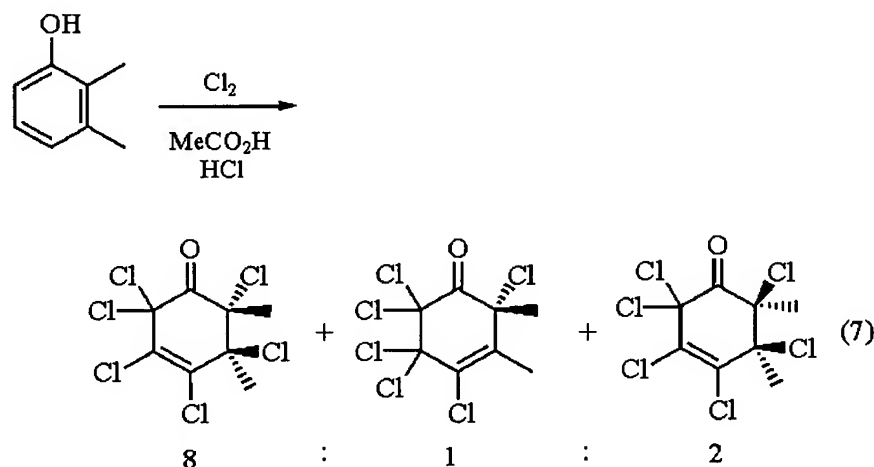
Chlorination of Aromatics.

Aromatic compounds may be chlorinated in the presence of Lewis acids like iron and iron(III) chloride. Low temperatures favor monochlorination, while high temperatures (150-190 °C) favor dichlorinated products.[11] The chlorination of alkylbenzenes in alcoholic media can result in higher yields of monochloro derivatives than when $FeCl_3$ is used.[12] Chlorine diluted in water converts tyrosine into 3-chloro-4-hydroxybenzyl cyanide (eq 6);[13] larger amounts of chlorine give 3,5-dichloro-4-hydroxybenzyl cyanide and 1,3-dichloro-2,5-dihydroxybenzene. The latter product can be converted into 2,6-dichloro-*p*-benzoquinone with additional aqueous chlorine.


$$(6)$$
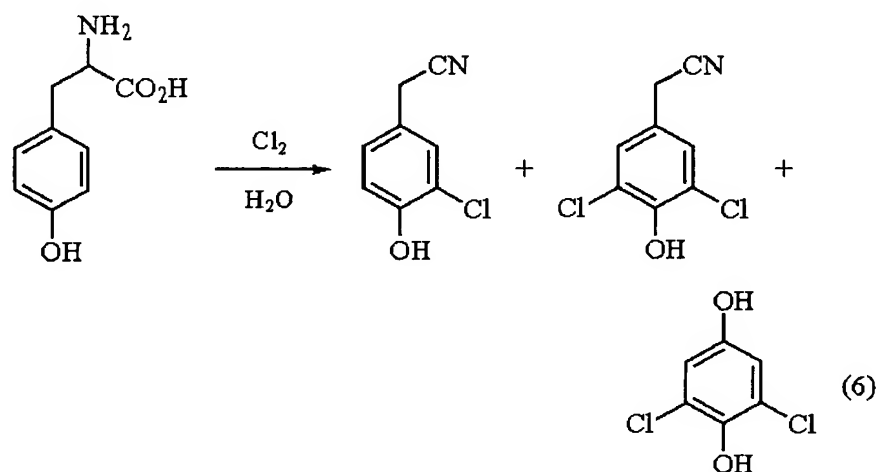
Toluene is chlorinated by the radical mechanism to give benzyl chloride, benzal chloride, and

benzotrichloride.[11] Sulfuryl chloride, **_t-Butyl Hypochlorite_**, **_Hydrogen Chloride_** (in the presence of a copper-salt catalyst), and **_N-Chlorosuccinimide_** have also been used to chlorinate aromatics.[11]

Chlorination of phenol yields 2-chlorophenol and 4-chlorophenol in a ratio of 0.45:0.49, which is higher than the *ortho/para* ratio obtained with *t*-butyl hypochlorite.[14] 4-Alkylphenols react with chlorine in various solvents to form mainly 4-alkyl-4-chlorocyclohexa-2,5-dienones (in yields of 19-100%) and substitution products.[15] Other chlorinating agents (alkyl hypochlorites, sulfuryl chloride, hypochlorous acid, and antimony pentachloride) have also been used, but they result in polychlorinated cyclohexadienones and cyclohexenones.[15] The chlorination of dimethylphenols with chlorine in acetic acid containing HCl results in polychlorinated cyclohexenones (eq 7).[16]

The α-monochlorination of alkyl aryl ketones by chlorine gas occurs readily in a variety of solvents (e.g. CH_2Cl_2, $CHCl_3$, CCl_4, HOAc).[17] α,α-Dichlorination of alkyl aryl ketones occurs with sodium acetate in refluxing acetic acid (5 h, 80-90% yield). Alternatively, DMF can be used as the catalyst (80-100 °C, 35-45 min) (eq 8).[18]


$$R = Me, Et, Pr, \textit{t-}Bu, Ph; R^1 = H, Cl, Br, Me$$
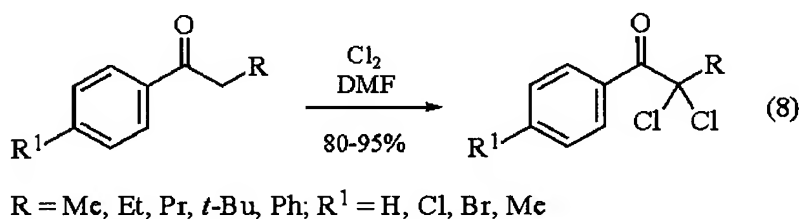
Chlorination of phenylenedibenzenesulfonamides by chlorine in nitrobenzene results in the formation of a mixture of dichloro derivatives.[19] The more useful tetrachloro derivative can be prepared by successive oxidations and additions of HCl, or in one step using Cl_2 in DMF (eq 9).[19] The temperature must be kept below 60 °C when Cl_2/DMF is used, or a runaway thermal reaction can result.[20]
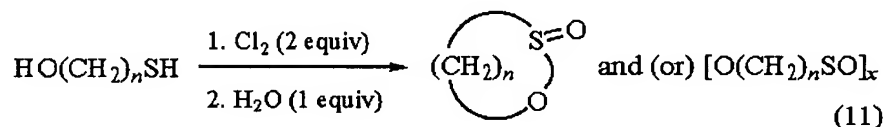
(9)
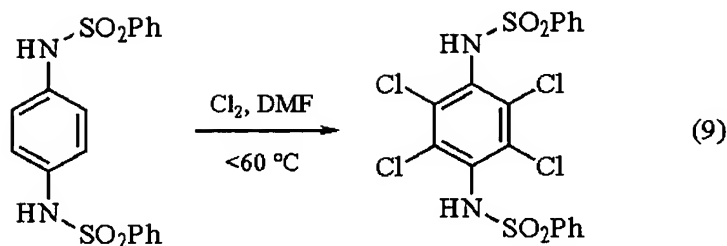
Chlorine has been used for the chlorination of heterocycles,[7i-k] but the varied reactivity of substrates makes discussion of these reactions too lengthy for this review.

Oxidation of Alcohols.

Alcohols have been oxidized with complexes of chlorine with dimethyl sulfide,[21] DMSO,[22] iodobenzene,[21] pyridine,[23] and HMPA.[21] Secondary hydroxyl groups are more readily oxidized than primary hydroxyl groups when the *Chlorine-Pyridine* (eq 10)[23] and chlorine-HMPA complexes[21] are used. The same results are obtained with 3-iodopyridine dichloride.[23]

(10)

69%   14%
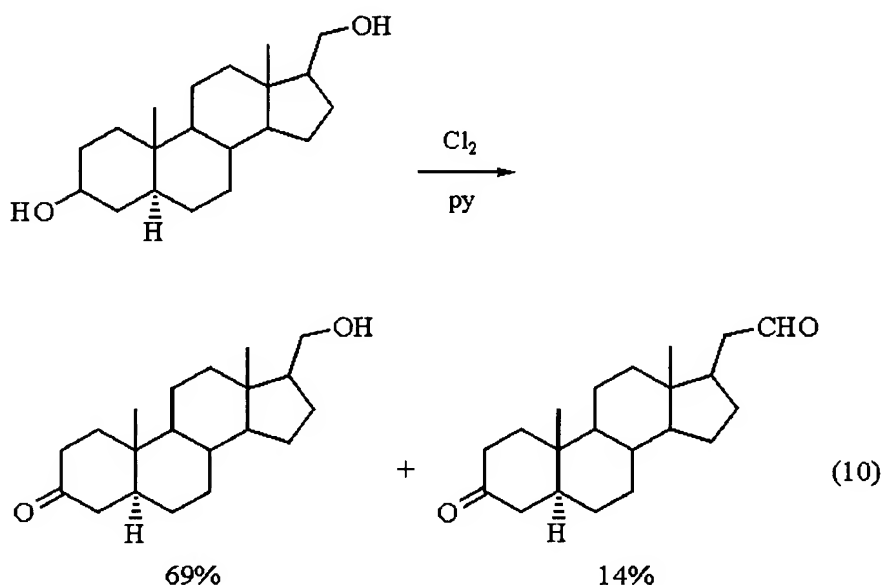
Hydroxythiols undergo chlorination reactions with Cl_2 in dichloromethane to form sultines and sulfinic esters after hydrolysis (eq 11).[24]

$$HO(CH_2)_nSH \xrightarrow[\text{2. } H_2O \text{ (1 equiv)}]{\text{1. } Cl_2 \text{ (2 equiv)}} (CH_2)_n \quad \text{and (or) } [O(CH_2)_nSO]_x$$

(11)

The oxidation of glycols usually results in C-C bond cleavage, but oxidation of the *s*-carbinol can be effected with a complex of a methyl sulfide (RSMe) and chlorine or NCS, or of DMSO and chlorine.[25] The tricyclic α-ketol (**2**) (eq 12) can be prepared from the glycol (**1**) using these reagents.[25]

(12)

(1)   (2)
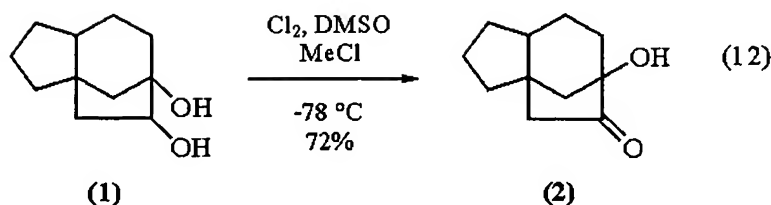
Chlorinolysis.

The C-C bond of short-chain hydrocarbons ($<C_3$ and any partially chlorinated derivatives) can be cleaved by chlorine at high temperatures to give chlorinated products. 1,2-Dichloroethane and 1,2-dichloropropane are cleaved by chlorine to give carbon tetrachloride and tetrachloroethylene with HCl as a byproduct.[11]

C-S Bond Cleavage.

The benzylic group of alkyl benzyl sulfides can be selectively cleaved by chlorine in aqueous acetic acid to give alkanesulfonyl chlorides (eq 13).[26]

$$PhCH_2SMe \quad \xrightarrow[75\%]{\substack{Cl_2 \\ AcOH}} \quad MeSO_2Cl + PhCH_2Cl \qquad (13)$$
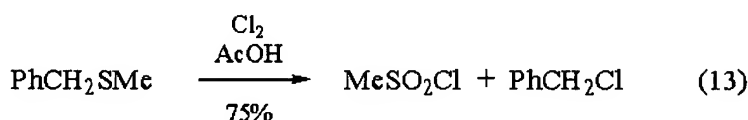
Excess chlorine has been used to cleave the secondary C-S bond in lactam (3) (eq 14) to give the azetidin-2-one (4) in nearly quantitative yield.[27] When *N*-acyl groups are present, as in eq 15, the nitrogen lone pair electrons are inhibited, so cleavage of the tertiary C-S bond is favored over the azetidine C-S bond.[27]

(3)   (4)
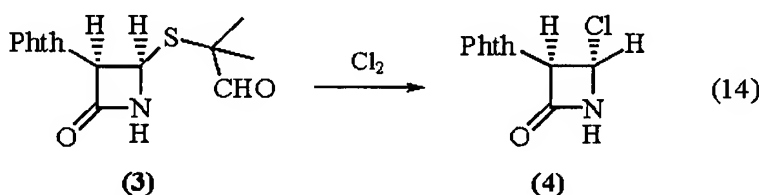
Phth = phthalimido
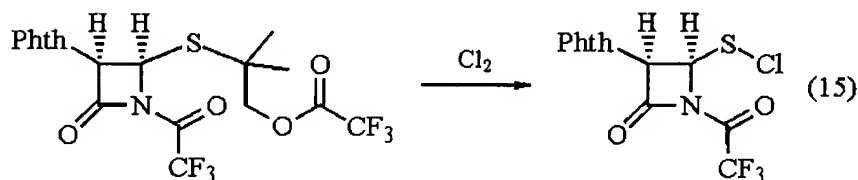
Other Reactions.

Chlorine and **Sodium Bromide** are used to produce **Bromine Chloride**, which can be used in bromination reactions which are faster than those with elemental **Bromine**, and which take place in aqueous solution rather than acidic solvents; the bromination of 4-nitrophenol to 2,6-dibromo-4-nitrophenol is one example.[28]
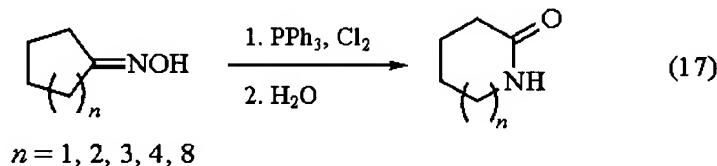
Thiocyanogen, prepared in anhydrous conditions from silver or lead thiocyanate and bromine, cannot be used for addition reactions with halogenated alkenes and is too expensive for most commercial processes.[29] Thiocyanogen can be prepared in a two-solvent system from *Sodium Thiocyanate* and chlorine.[29] The thiocyanogen is extracted into the toluene layer and can be used for addition reactions to vinyl halides in the synthesis of haloalkylene bisthiocyanates.

Several methods for the preparation of *Phosgene* are known, e.g. the gas-phase reaction of chlorine with carbon monoxide on activated carbon, the decomposition of trichloromethyl chloroformate, and the reaction of carbon tetrachloride with oleum.[30] Phosgene can be synthesized conveniently just before use by the reaction of chlorine with carbon monoxide in the presence of catalytic amounts of *t*-phosphine oxides, using carbon tetrachloride as the solvent.[30]
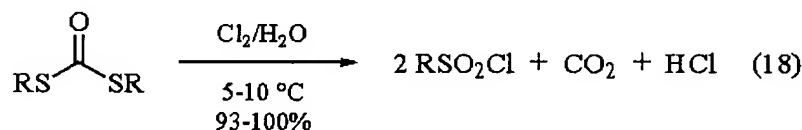
Chlorodimethylsulfonium chloride, generated in situ from *Dimethyl Sulfide-Chlorine*, is a useful reagent for the conversion of epoxides to α-chloro ketones (eq 16)[31] and of aldoximes to nitriles,[32] in the presence of tertiary amines. Bromodimethylsulfonium bromide, generated in the same way, can be used to form α-bromo ketones, but the yields are lower than those obtained for α-chloro ketones.[31]

$$\text{R-epoxide} \xrightarrow[\text{2. Et}_3\text{N}]{\text{1. Cl(SMe)}_2^+\text{Cl}^-} \text{R-C(=O)-CHR-Cl} \qquad (16)$$
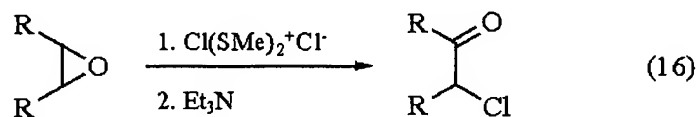
Chlorine and *Triphenylphosphine* are used in the synthesis of lactams from cycloalkanone oximes in high yields (eq 17).[33]

$$\text{(cycloalkanone)}=\text{NOH} \xrightarrow[\text{2. H}_2\text{O}]{\text{1. PPh}_3, \text{Cl}_2} \text{(lactam)} \qquad (17)$$

$$n = 1, 2, 3, 4, 8$$

Alkanesulfonyl chlorides, which are useful reagents and intermediates in organic synthesis, can be conveniently produced from dithiocarbonic acid esters (eq 18).[34]

$$\text{RS-C(=O)-SR} \xrightarrow[\substack{5\text{-}10\ °\text{C} \\ 93\text{-}100\%}]{\text{Cl}_2/\text{H}_2\text{O}} 2\,\text{RSO}_2\text{Cl} + \text{CO}_2 + \text{HCl} \qquad (18)$$

The indirect oxidation of trialkyl phosphites to trialkyl phosphates can be achieved in high yield and purity with chlorine in the corresponding alcohol (eq 19).[35] The indirect oxidation can also be effected by carbon tetrachloride, bromotrichloromethane, *Carbon Tetrabromide*, *Chloroform*, and hexachlorocyclopentadiene in alcohol.[35] Cyclic phosphites may undergo ring opening during reactions with chlorine, depending on the size of the ring and its degree of substitution.[7g]

$$(\text{RO})_3\text{P} + \text{Cl}_2 + \text{ROH} \xrightarrow{90\text{-}100\%} (\text{RO})_3\text{PO} + \text{RCl} + \text{HCl} \qquad (19)$$
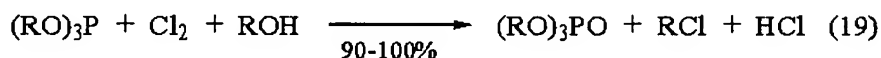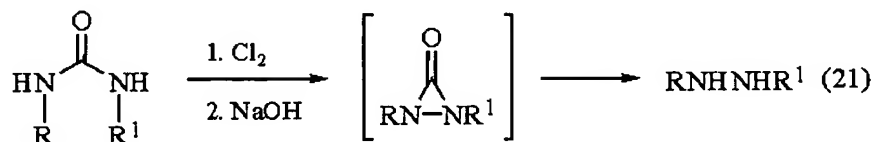
Cyclooctanone oxime can be synthesized from cyclooctane by a photochemical reaction with chlorine and nitrous oxide (eq 20).[36] The oxime hydrochloride intermediate is converted into the oxime by aqueous

sodium hydroxide.

(20)
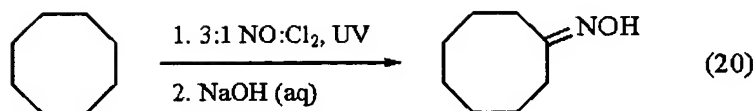
Chlorine can be used for the synthesis of hydrazines from ureas, via diaziridinone intermediates (eq 21).[7h]

Related Reagents.

Bromine; *Chlorine–Chlorosulfuric Acid*; *Dimethyl Sulfide–Chlorine*; *Chlorine–Pyridine*; *Iodine*;
Sulfuryl Chloride.

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Bromine[1]

$$Br_2$$

[7726-95-6] · Br_2 · Bromine · (MW 159.81)

(powerful brominating and oxidizing agent; can initiate/participate in ring cleavage and rearrangement)

Physical Data: mp -7 °C; bp 59 °C; d 3.12 g cm^{-3}.

Solubility: sol H_2O, acetic acid, alcohol, ether, chloroform, carbon tetrachloride, carbon disulfide, hydrocarbon solvents (pentane, petroleum ether).

Form Supplied in: dark, red-brown, volatile liquid; also available as a 1 M solution in carbon tetrachloride.

Analysis of Reagent Purity: by iodometric titration.[79]

Purification: several methods have been described.[80]

Handling, Storage, and Precautions: bromine is an extremely corrosive and toxic reagent in both liquid and vapor form. As a liquid, it produces painful burns and blisters when spilled on the skin. Such burns should be flushed with water and neutralized with a 10% solution of sodium thiosulfate in water. Medical attention should be sought immediately. Protective clothing is therefore a must, including laboratory coat and apron, protective gloves, and a full-face respirator equipped with a NIOSH-approved organic vapor-acid gas canister. Bromine should be stored in a cool, dry area. It is incompatible with combustibles, liquid ammonia, alkali hydroxides, metals (including aluminum, mercury, magnesium, and titanium), and some types of rubber and plastic.[2] Use in a fume hood.

Halogenations.

Bromine is a very powerful brominating agent that has found utility in a variety of systems. While the bromination of alkanes is usually not a viable synthetic method,[3] alkylbenzenes can be brominated at the benzylic position under radical conditions (eq 1).[4] *N-Bromosuccinimide* (NBS) can also be used for this transformation.

$$(1)$$
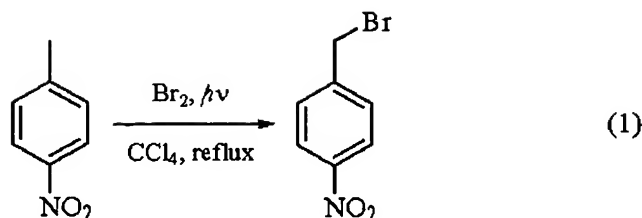
Electrophilic aromatic substitution occurs in the presence of Lewis acids to provide brominated aromatics.[5] Monobromination usually occurs due to the deactivating nature of the bromine. However, highly reactive aromatics, such as phenols, anilines, and polyalkylbenzenes, are frequently polybrominated, even in the absence of catalysts.

Bromine has been used in the bromination of heterocycles. However, the unique reactivity patterns of each heterocyclic ring system create a discussion beyond the scope of this review. The reader is directed to reviews on the subject.[1a,6]

The addition of bromine to alkenes[7] proceeds with formation of the cyclic bromonium ion (1), which can then be intercepted by an anionic species (Y⁻), to give the product derived from *anti* addition (eq 2). In the case of bromine itself, this gives rise to *trans* vicinal dibromides (eq 2; Y = Br). Variations from ideality are not uncommon due to weakened, unsymmetrical bridging in the bromonium ion (eq 3),[8] transannular interactions (eq 4),[9] and substrates susceptible to rearrangements. Brominations in the presence of crown ethers[10] and zeolites[11] have been investigated to improve selectivity. Conjugated dienes give predominantly 1,4-addition, while alkynes are less susceptible to electrophilic attack.[12]


$$(2)$$

$$(3)$$

$$(4)$$
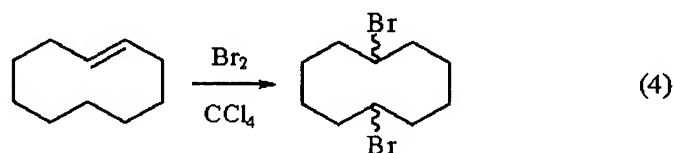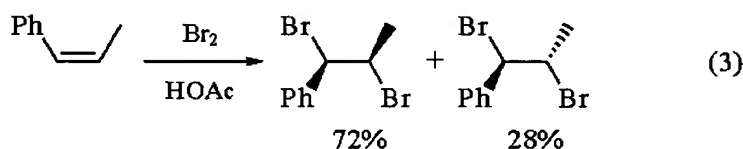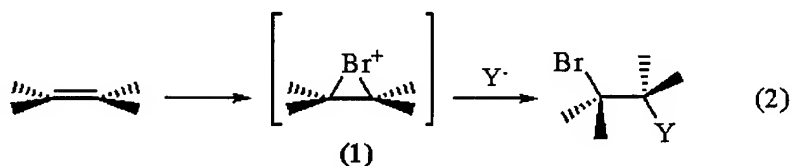
The addition of bromine to alkenes has been used as the first step in the oxidation of alkenes to 1,3-butadienes (eqs 5 and 6).[13,14] Alkenes can also be protected[15] or purified[16] by bromination and subsequent regeneration of the double bond.


$$(5)$$

$$\text{(6)}$$
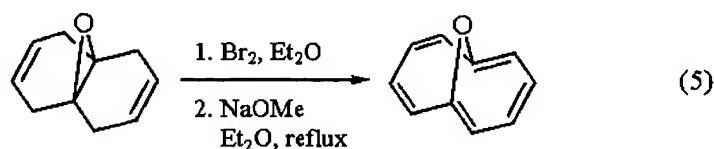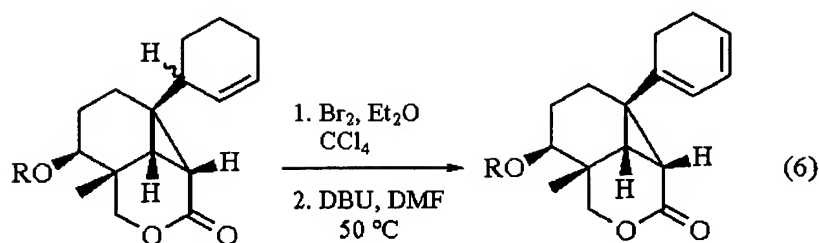
Alkenes bearing an electron-withdrawing group at one terminus are frequently converted to the α-bromo analogs via a bromination/dehydrobromination sequence (eqs 7 and 8).[17,18]

$$\text{(7)}$$

$$\text{(8)}$$
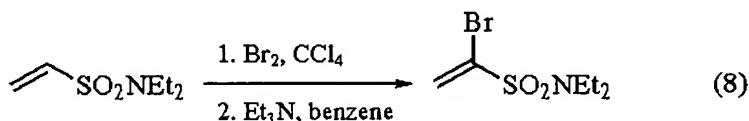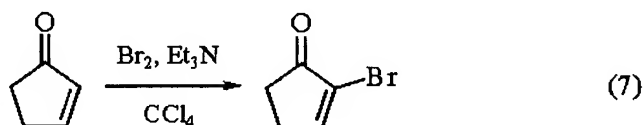
Cyclic bromonium ions (1) can be opened by a variety of other nucleophiles. Thus bromination of alkenes in aqueous systems can lead to bromohydrins. However, NBS has been shown to be superior to bromine for this transformation, presumably due to the minimization of competing bromide ion in the reaction mixture.[19] Alcohols react to give vicinal bromo ethers, in both inter- and intramolecular fashion (eq 9).[20]

$$\text{(9)}$$
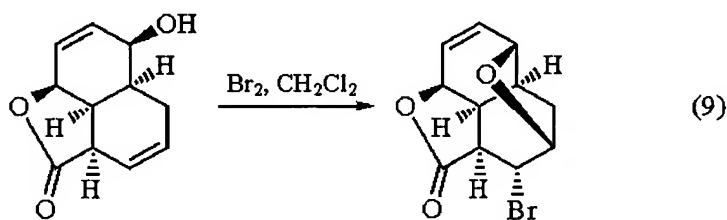
Bromolactonization of alkenic acids has been the subject of extensive investigation.[21] Cyclizations can be performed on the carboxylic acid salts as well as the free acids. Thallium(I) salts have proven to be especially efficacious.[21b,22] Treatment of the mercury(II) salts with bromine proceeds via a radical mechanism and provides the expected products in substrates where normal bromolactonization conditions lead to rearrangement (eq 10).[23] Other sources of electrophilic bromine can also give different products (eq 11).[21b]

(10)

(11)
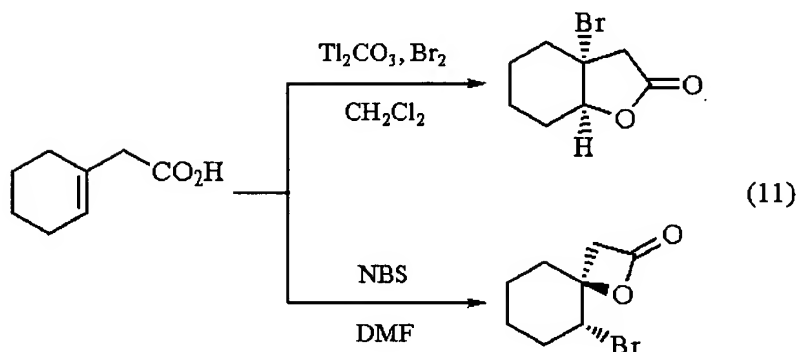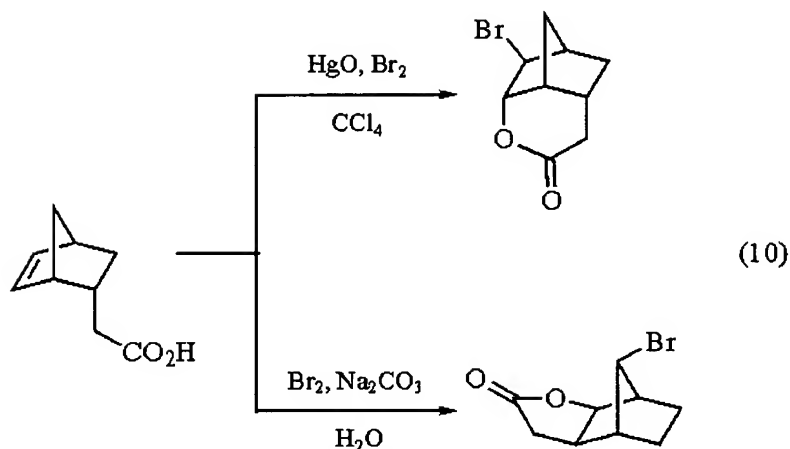
The enol lactonization of alkynic acids can be performed to give either the (*E*)- or (*Z*)-bromo enol isomers depending on reaction conditions (eq 12).[24]

(12)
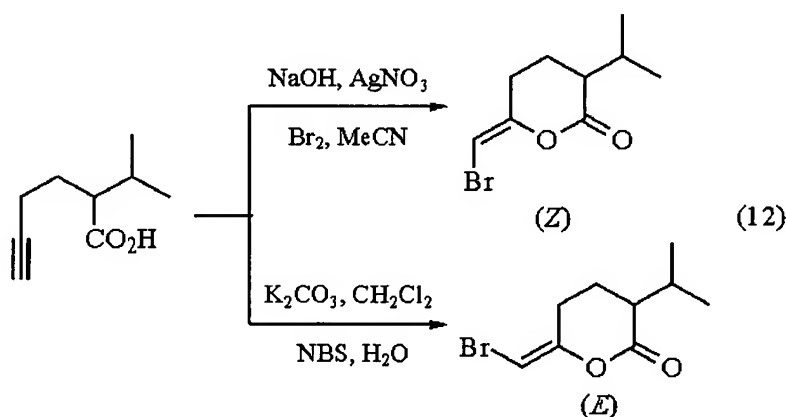
Alkenic amides cyclize under standard conditions to form lactones rather than lactams.[25] Bromolactamization can be achieved, however, by introduction of substituents on the amide nitrogen that serve to lower its pK_a (eqs 13 and 14).[26,27]

(13)

$$(14)$$

$$R = Me, \quad \textit{cis:trans} = 23:77$$
$$R = CbzNH, \quad \textit{cis:trans} = 70:30$$
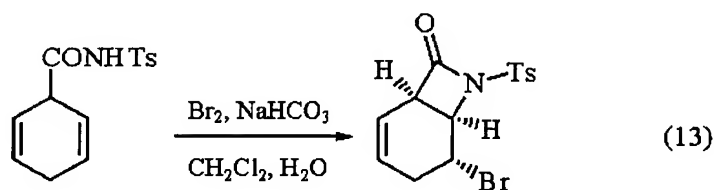
Electron-rich alkenes, such as enol ethers[28] and enamines,[29] can be brominated to furnish the β-bromo compounds (eq 15).

$$(15)$$

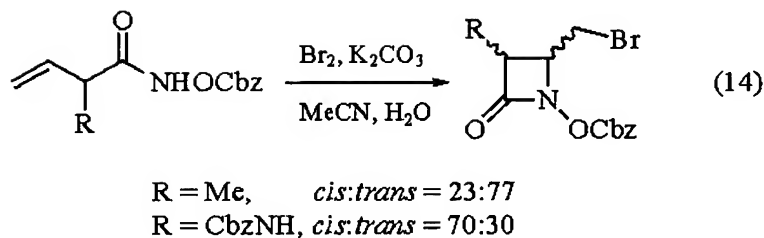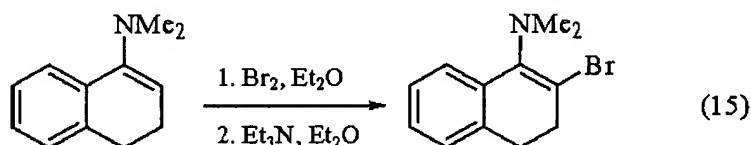Bromine has been used for brominations α to carbonyl groups.[30] Carboxylic acids are brominated in the presence of phosphorus or phosphorus trihalides in the classical Hell-Volhard-Zelinski reaction (eq 16).[31] Variations on this include brominations in thionyl chloride[32] and in polyphosphoric acid.[33] The less reactive carboxylic esters are frequently converted to the acid halide, α-brominated, and subsequently re-esterified in one pot.[34,35]

$$(16)$$
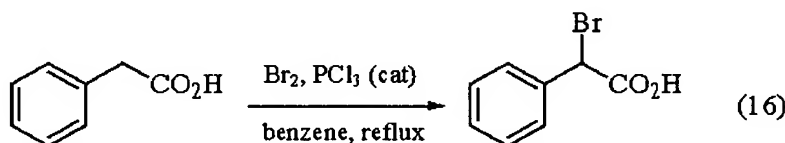
The bromination of ketones is believed to occur via acid-catalyzed enolization, followed by electrophilic attack on the enol form.[30] Unsymmetrical ketones can give rise to mixtures of bromo ketones due to mixtures of enols, and several approaches to overcome this shortcoming have been reported. Radical bromination in the presence of epoxides (as acid scavengers) allows for substitution at the more highly substituted position (eq 17).[36] Silyl enol ethers of aldehydes and ketones react with bromine (or NBS) to give the α-brominated carbonyl compounds (eq 18).[37] This, combined with the ability to regiospecifically prepare silyl enol ethers (kinetic vs. thermodynamic), makes for an extremely useful technique for the preparation of α-bromo carbonyl compounds.

$$(17)$$

*h*v, epoxide   100: 0
dark, no epoxide   60:40

$$(18)$$

Sulfoxides are best α-brominated with a combination of bromine and NBS in pyridine.[38]
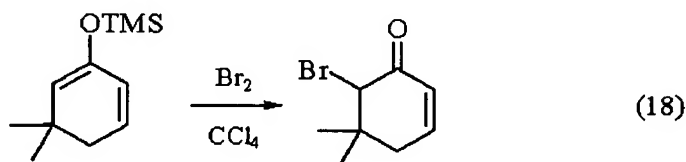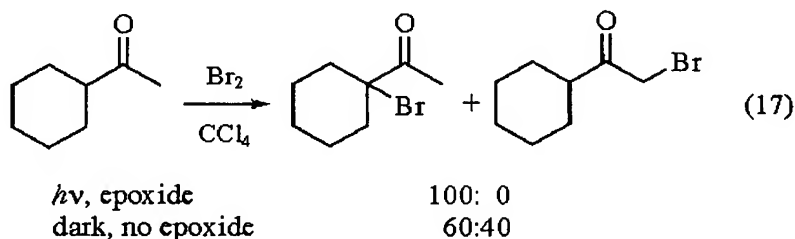
Bromine has been used in the halogenation of organometallic reagents. Organomagnesium,[39] organolithium,[40] and organoaluminum[41] reagents react to give the compounds in which the metal has been replaced by bromine. Organoboranes can react with bromine in several ways. Bromination in the presence of sodium methoxide gives the corresponding alkyl bromides.[42] Photobromination (in the absence of strong base) gives an initial α-bromo organoborane that can either give the corresponding alkyl bromide[43] or rearrange to a new organoborane.[44] Organoboranes can also be converted to alkyl bromides in aqueous media.[45] Alkenic bromides have been prepared from alkenylboronic esters with inversion of configuration (eq 19).[46]

$$\begin{array}{ccc} C_5H_{11} \quad C_5H_{11} & \quad 1.\ Br_2,\ CH_2Cl_2 & C_5H_{11} \quad Br \\ \diagdown \diagup & \xrightarrow{\hspace{2cm}} & \diagdown \diagup \\ B(OMe)_2 & 2.\ NaOMe,\ MeOH & C_5H_{11} \end{array} \qquad (19)$$

Enolates of ketones[47] and esters[48] can be brominated by treatment with bromine (eq 20), as can the anions of terminal alkynes.[49] The high reactivity of bromine, however, is sometimes a problem; milder sources of electrophilic bromine (such as *1,2-Dibromoethane*) are occasionally used in its place.

$$\xrightarrow[\text{2. }Br_2]{\text{1. LDA, THF}} \qquad (20)$$

Oxidations.

Bromine reacts with secondary alcohols to give ketones. Since ketones are subject to bromination themselves (see above), the α-bromo ketones can sometimes be undesirable byproducts. However, in cases where there are no α-protons, this can provide an excellent method of oxidation (eq 21).[50]

$$\xrightarrow[\text{CCl}_4,\ \text{reflux}]{Br_2} \qquad (21)$$

Primary alcohols are oxidized to either aldehydes or, more commonly, esters. An especially attractive corollary to this involves the oxidation of acetals to esters (eq 22).[51]

$$C_7H_{15} \xrightarrow[\text{MeCN, H}_2\text{O}]{Br_2} C_7H_{15}\text{C(O)O}\diagdown\diagdown Br \qquad (22)$$

The addition of coreactants has provided a number of selective bromine-based oxidants. Both bromine/*Hexamethylphosphoric Triamide* (HMPA)[52] and bromine/*Bis(tri-n-butyltin) Oxide* (HBD)[53]

have shown a preference for the oxidation of secondary vs. primary alcohols (eq 23), while bromine/nickel carboxylates[54] convert 1,4-diols to γ-butyrolactones by selective oxidation of the primary alcohols (eq 24).

$$\text{OH} \quad \text{OH} \quad \xrightarrow[\text{CH}_2\text{Cl}_2]{\text{Br}_2,\ (\text{Bu}_3\text{Sn})_2\text{O}} \quad \text{O} \quad \text{OH} \qquad (23)$$

$$\text{C}_6\text{H}_{13} \quad \text{OH} \quad \text{OH} \quad \xrightarrow[\text{MeCN}]{\begin{array}{c}\text{Br}_2\\ \text{Ni}^{II}\text{2-ethyl-}\\ \text{hexanoate}\end{array}} \quad \text{C}_6\text{H}_{13} \quad \text{O} \quad \text{O} \qquad (24)$$
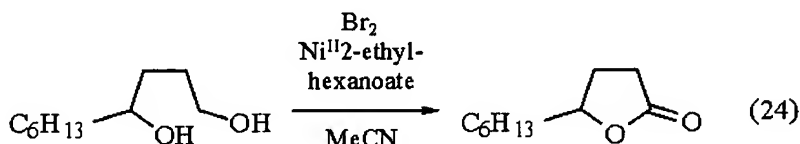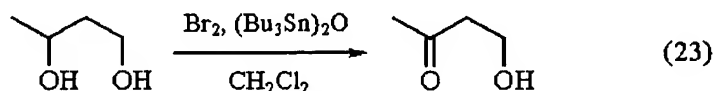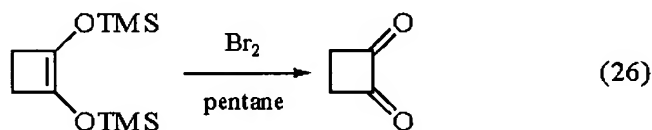
Tetrahydrofurans have been prepared from alcohols or diols by bromine/silver(I) salts (eq 25)[55] or bromine/DMSO,[56] respectively.
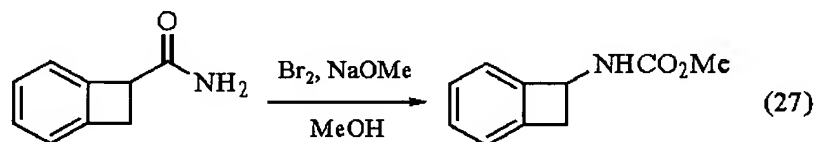
$$\xrightarrow[\text{pentane}]{\text{Br}_2,\ \text{Ag}_2\text{CO}_3} \qquad (25)$$

$$cis{:}trans = 53{:}47$$
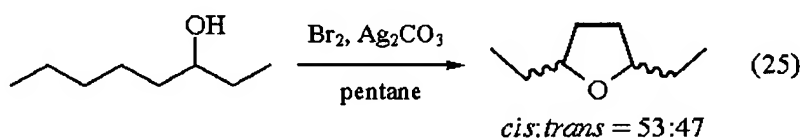
Bromine has demonstrated its superiority in the oxidation of enediol bis-trimethylsilyl ethers to α-diketones (eq 26).[57]

$$\begin{array}{c}\text{OTMS}\\ \\ \text{OTMS}\end{array} \xrightarrow[\text{pentane}]{\text{Br}_2} \begin{array}{c}\text{O}\\ \\ \text{O}\end{array} \qquad (26)$$

A number of other functional groups are oxidized by bromine; however, they do not appear to have gained widespread use. These include cyclohexenones,[58] ethers,[59] hydrazines,[60] oximes,[61] tertiary amines,[62] thiols,[63] sulfides,[64] and organoselenium reagents.[65]

Rearrangements.

Bromine reacts with a number of functional groups to effect bond cleavage or other skeletal rearrangements. In the classical Hofmann rearrangement,[66] treatment of primary amides with bromine in the presence of base gives isocyanates, carbamates, or amines, depending on the reaction conditions (eq 27).[67]

$$\begin{array}{c}\text{O}\\ \\ \text{NH}_2\end{array} \xrightarrow[\text{MeOH}]{\text{Br}_2,\ \text{NaOMe}} \begin{array}{c}\\ \text{NHCO}_2\text{Me}\end{array} \qquad (27)$$

In the Hunsdiecker reaction,[68] treatment of silver salts of carboxylic acids with bromine furnishes the alkyl(aryl) bromides with one less carbon atom. Improvements that do not require the preparation of the dry silver salts include the use of mercury(II) salts (Cristol-Firth modification) (eq 28),[69] thallium(I) salts,[70] and photostimulation.[71]

$$\triangleright\!-\!CO_2H \xrightarrow[\text{tetrachloroethane}]{Br_2,\ HgO} \triangleright\!-\!Br \qquad (28)$$
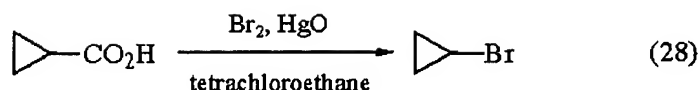
Three-membered rings are especially susceptible to reaction with bromine. Cyclopropanes are opened to give 1,3-dibromopropanes,[72] while cyclopropenylethanol derivatives rearrange in the presence of bromine to give 3-methylenetetrahydrofurans (eq 29).[73] Trimethylsilyl cyclopropyl ethers are opened to give β-bromo ketones (eq 30).[74] Epoxides can give either bromohydrins[75] or α-bromo ketones,[76] depending on the reaction conditions.

$$(29)$$

$$(30)$$
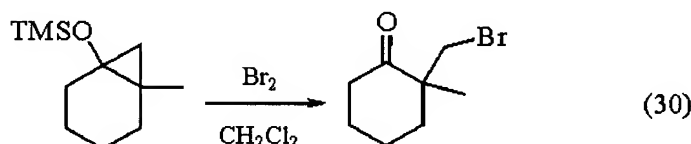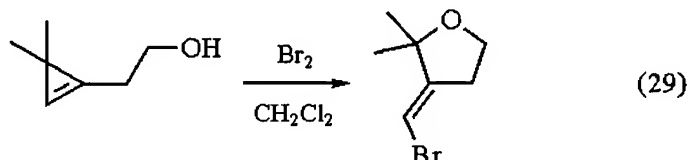
Mercury(II)-mediated cyclization of dienes allows access to bromine-containing natural products.[77] Thus, in the synthesis of aplysistatin, the key step was the cyclization of an acyclic precursor to the required bromoperhydro[1]benzoxepine ring system (eq 31).[78]

$$(31)$$
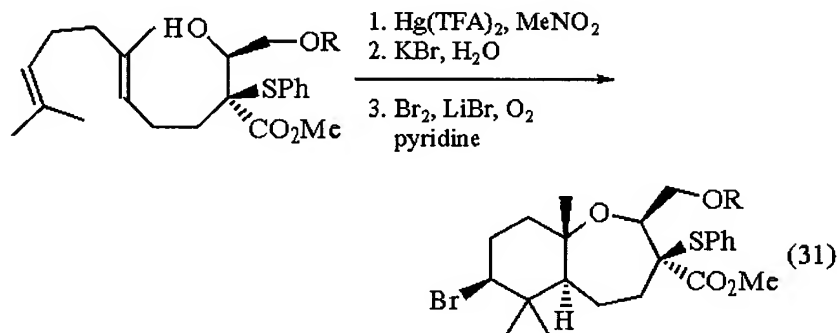
Related Reagents.

Bromine-t-Butylamine; Bromine Chloride; Bromine-1,4-Diazabicyclo[2.2.2]octane; Bromine-1,4-Dioxane; Bromine-Silver(I) Oxide; Bromine-Triphenyl Phosphite; N-Bromosuccinimide; N-Bromosuccinimide-Dimethylformamide; N-Bromosuccinimide-Dimethyl Sulfide; N-Bromosuccinimide-Sodium Azide; Copper(II) Bromide; Hydrobromic Acid; Mercury(II) Oxide-Bromine; Phosphorus(III) Bromide; Pyridinium Hydrobromide Perbromide; Sodium Bromide; Thallium(III) Acetate-Bromine.

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Iodine

$$\boxed{I_2}$$

[7553-56-2] · I_2 · Iodine · (MW 253.80)

(electrophilic reagent that adds to alkenes[1] and alkynes[2] to give diiodides; alkenyl carboxylic acids react to give iodolactones[3] and alkenyl amides lead to iodolactams;[4] dehydrogenates amines[5] and reacts with ketones, in the presence of base, to give α-iodo ketones;[6] carboxylic acids are converted to α-iodo acid derivatives[7] and carbanions react to give the substituted iodides;[8] organoboranes can give alkyl iodides[9] and vinylboranes lead to substituted alkenes;[10] important spotting reagent for TLC analysis[11])

Physical Data: mp 113.6 °C; bp 185.24 °C; d 4.930 g cm^{-3}; vapor pressure 0.31 mmHg at 25 °C.

Solubility: the solubility of iodine, expressed in g/kg of solvent at 25 °C is: H_2O, 0.34; benzene, 164.0; CCl_4, 19.2; $CHCl_3$, 49.7; ethyl acetate, 157; ethanol, 271.7; diethyl ether, 337.3; *n*-hexane, 13.2; toluene, 1875.[12] Soluble glacial acetic acid; relatively insol dichloromethane.

Form Supplied in: the natural abundance isotope is ^{127}I. It is a massive bluish-black solid. When sublimed it forms near opaque, doubly refractory orthorhombic crystals that have a metallic luster. Heating iodine generates a violet-colored vapor. Commercially available in >99.5% purity, with bromine and chlorine the primary contaminants. Natural abundance iodine is diatomic, I-I.

Preparative Methods: commercially available but can be prepared by the reaction of potassium iodide and copper(II) sulfate.[13] It is also prepared by chlorination of natural brines or by treatment of brine with silver nitrate and then iron(II) iodide, followed by addition of chloride to liberate iodine.[14]

Purification: vacuum sublimation.

Handling, Storage, and Precautions: somewhat corrosive.[15] It is stored in a dark bottle or jar, at ambient temperatures. Iodine vapors have a sharp characteristic odor and they are irritating to eyes, skin, and mucous membranes (lachrymatory). Prolonged exposure should be avoided. Ingestion of large quantities can cause abdominal pain, nausea, vomiting, and diarrhea. If 2-3 g of iodine are ingested, death may occur.

Introduction.

Diatomic iodine (I_2) is a member of the halogen family that is widely used in organic chemistry. Iodine is less electronegative than the other halogens, and iodides are generally less stable than other halides.[16] Oxides of iodine and compounds where iodine is in a positive valence state are much more stable than the other halogens. Iodine forms binary compounds with all elements except sulfur, selenium, and the noble gases, although it does not react directly with carbon, nitrogen, or oxygen.[15] Its applications in organic chemistry range from detection of organic molecules in TLC, to addition reactions with unsaturated molecules, to reactions as an electrophilic agent with nucleophilic species. Iodine is used not only as an agent for incorporating an iodine atom but also as an oxidizing agent, a dehydrogenation agent, and as a radiolabel in many biologically important systems.

One of the most common uses of iodine is as a spotting agent for the detection of organic molecules in TLC.[11] Many organic molecules either adsorb iodine vapors or react with iodine vapor to produce a visible spot on the TLC plate. In general, basic compounds and reducing compounds pick up iodine vapors very well, but acidic compounds and oxidizing compounds do not.[11] Many natural products can be detected via TLC, including steroids,[17] phenolic compounds,[18] and alkaloids.[19]
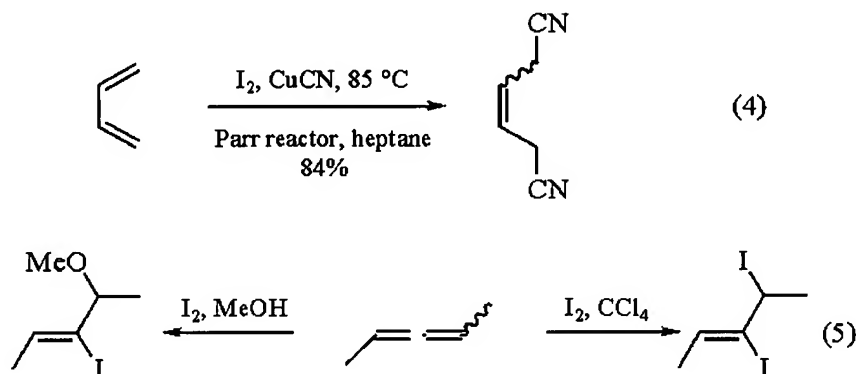
Addition to Alkenes.

Iodine is a highly polarizable molecule that behaves as electrophilic iodine (I^+) in the presence of a suitable Lewis base, such as an alkene or an alkyne. When an alkene reacts with molecular iodine, a characteristic iodonium ion is formed, and subsequent reaction with the nucleophilic gegenion (I^-) leads to the vicinal diiodide. There are many examples of this type of reaction. Addition of iodine to cyclohexene to give trans-1,2-diiodocyclohexane is a simple example (eq 1).[1] The reaction is believed to involve a radical intermediate, evidenced by formation of dimeric coupling products in many alkene iodination reactions. Reaction of styrene with iodine (neat), for example, gives not only 1,2-diiodo-2-phenylethane but also 1,4-diiodo-2,3-diphenylbutane as a minor product (eq 2).[20]


$$(1)$$

$$(2)$$
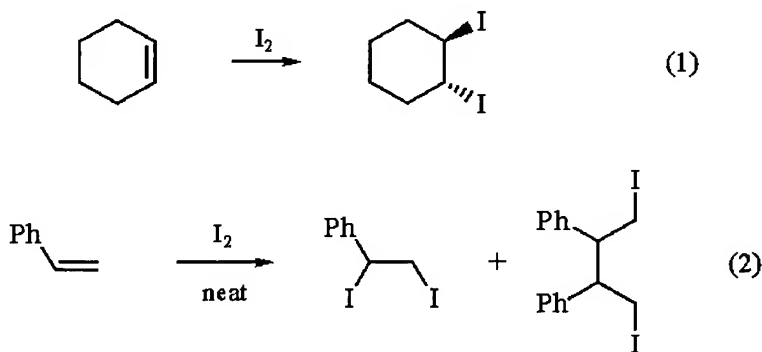
The iodine reaction can be modified by addition of other reagents, such as methanol, to produce iodo ethers. When iodine in methanol is reacted with cyclohexene, in the presence of *Cerium(IV) Ammonium Nitrate* (CAN), a 92% yield of 2-methoxy-1-iodocyclohexane is obtained (eq 3).[21a] Similar results are obtained when iodine and *Copper(II) Acetate* are used.[21b]

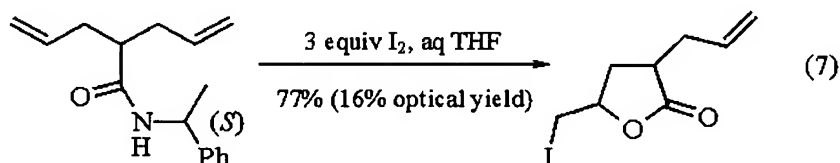$$\text{I}_2, \text{CAN, MeOH} \quad 50 \text{ °C, 6 h} \quad 92\% \tag{3}$$
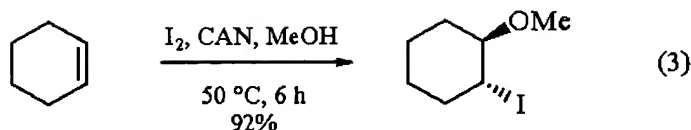
Iodine reacts with dienes to form a mixture of 1,2-diiodoalkenes and 1,4-diiodoalkenes. When done in the presence of **Copper(I) Cyanide**, the 1,4-addition product predominates and 1,3-butadiene thus reacts to give an 84% yield of 1,4-dicyano-2-butene (eq 4).[22] Allenes react with iodine to give diiodides. When 2,3-pentadiene reacts with iodine in carbon tetrachloride, 2,3-diiodo-3-pentene is formed (eq 5).[23] When the reaction is done in methanol, however, 3-methoxy-2-iodo-3-pentene is the product.

$$\text{I}_2, \text{CuCN, 85 °C} \quad \text{Parr reactor, heptane} \quad 84\% \tag{4}$$

$$\text{I}_2, \text{MeOH} \qquad \text{I}_2, \text{CCl}_4 \tag{5}$$
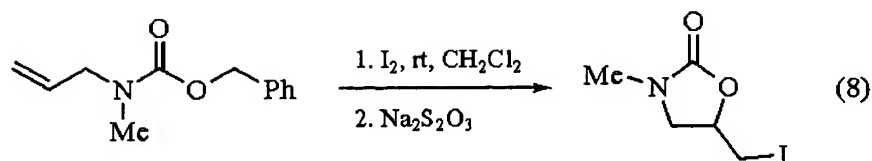
There are two very interesting and useful variations of the fundamental addition reactions to alkenes: iodolactonization[3] (to form iodolactones) and iodolactamization (to produce iodolactams). When an alkenyl acid reacts with iodine in the presence of a base (such as sodium bicarbonate), the initially formed iodonium ion reacts with the carboxylate anion (generated in situ) to form the iodolactone (eq 6).

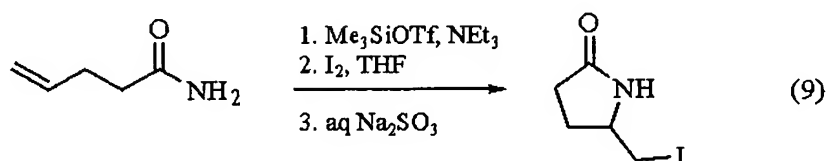$$\text{I}_2, \text{NaHCO}_3 \tag{6}$$
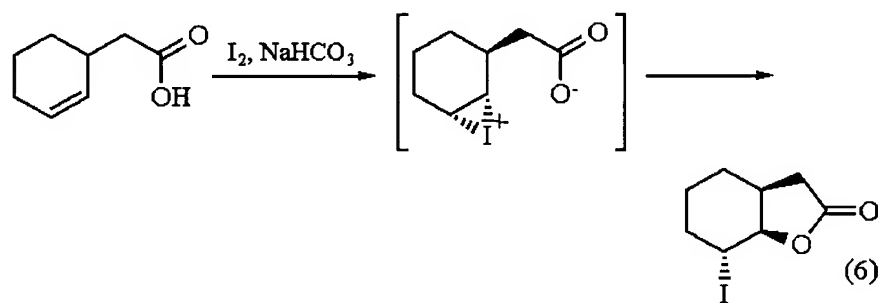
Lactones are also formed when iodine reacts with alkenyl amides or alkenyl carbamates. In initial studies, amides led to the formation of lactones whereas carbamates gave oxazolidinones. When N-(S)-phenethyl-2-allyl-4-pentenamide reacts with 3 equiv of iodine in aqueous THF, a 77% yield of 2-allyl-5-iodomethyl-δ-butyrolactone is obtained (16% optical purity) (eq 7).[24] Similarly, reaction of N-Cbz-N-methyl-2-propenamine with iodine in dichloromethane leads to a 95% yield of N-methyl-4-iodomethyl-2-oxazolidinone (eq 8).[25]

$$3 \text{ equiv I}_2, \text{ aq THF} \quad 77\% \text{ (16\% optical yield)} \tag{7}$$

$$\text{(allyl-N(Me)-C(=O)-O-CH}_2\text{Ph)} \xrightarrow[\text{2. Na}_2\text{S}_2\text{O}_3]{\text{1. I}_2,\ \text{rt, CH}_2\text{Cl}_2} \text{(Me-N oxazolidinone-CH}_2\text{I)} \tag{8}$$
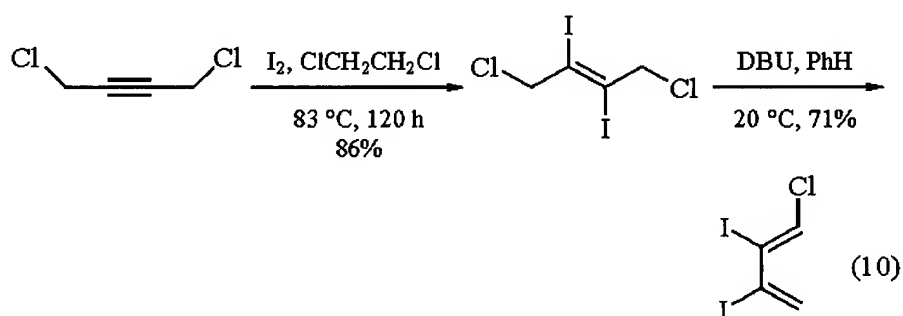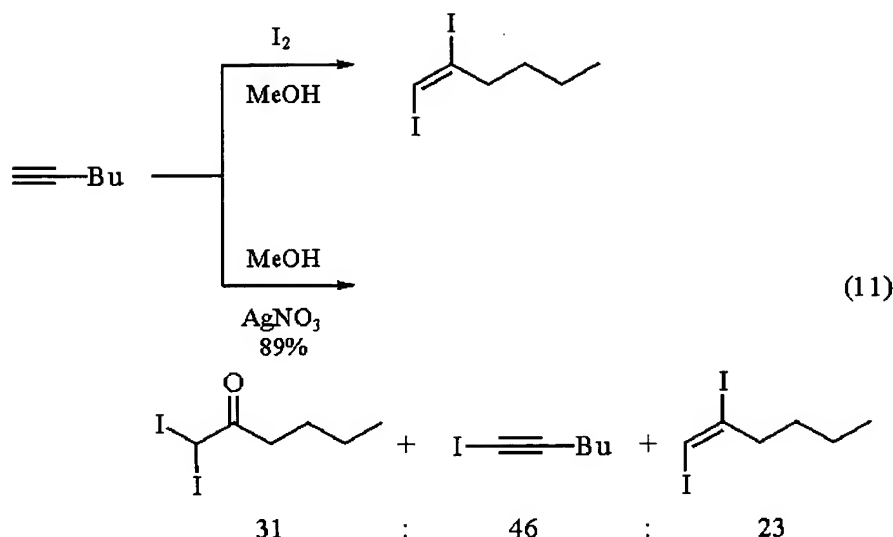
The more difficult lactam forming reaction (iodolactamization) can be accomplished by treatment of primary alkenyl amides with **Trimethylsilyl Trifluoromethanesulfonate**, followed by iodination, as in the conversion of 4-pentenamide to 5-iodomethyl-2-pyrrolidinone in 68% yield (eq 9).[4] There are several other cyclization reactions that are initiated by the reaction of iodine with an alkene, in the presence of a nucleophilic atom elsewhere in the molecule.[26]

$$\text{(4-pentenamide, NH}_2\text{)} \xrightarrow[\text{3. aq Na}_2\text{SO}_3]{\begin{array}{l}\text{1. Me}_3\text{SiOTf, NEt}_3\\ \text{2. I}_2,\ \text{THF}\end{array}} \text{(pyrrolidinone NH, CH}_2\text{I)} \tag{9}$$

Addition to Alkynes.

Iodine undergoes addition reactions with alkynes as well as alkenes, although the reaction is generally more sluggish. Reaction of 1,4-dichloro-2-butyne with iodine, for example, requires 1,2-dichloroethane as a solvent and heating to 83 °C for 120 h to give (*E*)-1,4-dichloro-2,3-diiodo-2-butene (eq 10).[27] Treatment of this alkene with **1,8-Diazabicyclo[5.4.0]undec-7-ene** leads to formation of iododienes. Another example is 1-hexyne, which reacts with iodine in methanol to produce (*E*)-1,2-diiodo-1-hexene (eq 11).[2] When **Silver(I) Nitrate** is added to this mixture, however, a mixture of 1,1-diiodo-2-hexanone, 1-iodo-1-hexyne, and (*E*)-1,2-diiodo-1-hexene is formed (31%, 46%, 23% yields).[15]

$$\text{(Cl-CH}_2\text{-C}\equiv\text{C-CH}_2\text{-Cl)} \xrightarrow[\begin{array}{c}\text{83 °C, 120 h}\\ \text{86\%}\end{array}]{\text{I}_2,\ \text{ClCH}_2\text{CH}_2\text{Cl}} \text{(Cl-CH}_2\text{-CI=CI-CH}_2\text{-Cl)} \xrightarrow[\text{20 °C, 71\%}]{\text{DBU, PhH}} \tag{10}$$

$$(11)$$

$$31 \quad : \quad 46 \quad : \quad 23$$

Cleavage of Cyclopropanes.

Iodine also reacts with cyclopropanes, leading to ring opening and formation of a diiodide.[28] The cyclopropane ring in benzocyclopropanes, for example, reacts with iodine to produce the diiodide (eq 12). Cyclopropylcarbinyl systems are opened by iodine, and when a leaving group is available, such as trimethyltin, an alkenyl iodide is formed (eq 13).

$$(12)$$

$$(13)$$
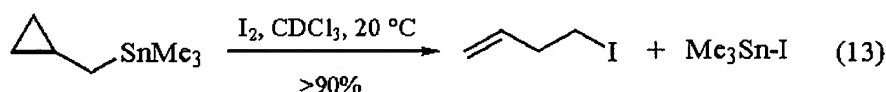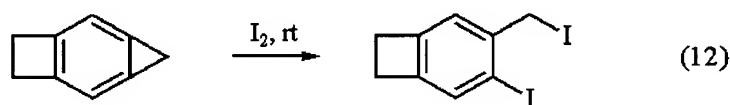
Conversion of Alcohols to Iodides.

Alcohols react with iodine and red phosphorus to produce a phosphorus iodide, in situ. Phosphorus iodides have poor shelf lives (they are unstable and decompose under mild conditions) and are prepared immediately prior to use. An example is the conversion of cetyl alcohol to cetyl iodide in 85% yield (eq 14).[29] This is the most common method for the conversion of aliphatic alcohols to aliphatic iodides.

$$(14)$$
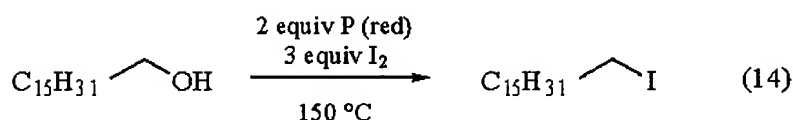
Reaction with Amines.

Dehydrogenation is another important reaction of iodine, and it is particularly useful for generation of enamines. Reaction of nuciferine with iodine, in dioxane containing sodium acetate, leads to an 87% yield of the enamine dehydronuciferine (eq 15).[30] Amines in general lead to enamines, as in the conversion of triethylamine to N,N-diethylvinylamine (eq 16).[5] This reaction can be applied to many systems.[31] For

systems that do not contain an amino moiety, e.g. arenes such as ethylbenzene, a flow reactor and high temperatures (650 °C) are required for dehydrogenation. This particular example uses a molten *Lithium Iodide* reactor to convert ethylbenzene to the alkene product, styrene, in 96% yield (eq 17).[32]


$$(15)$$

$$(16)$$

$$(17)$$
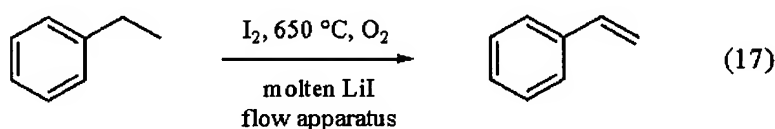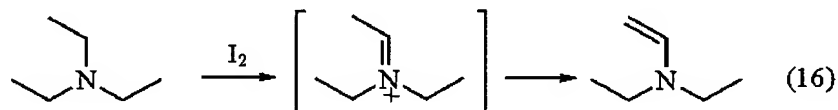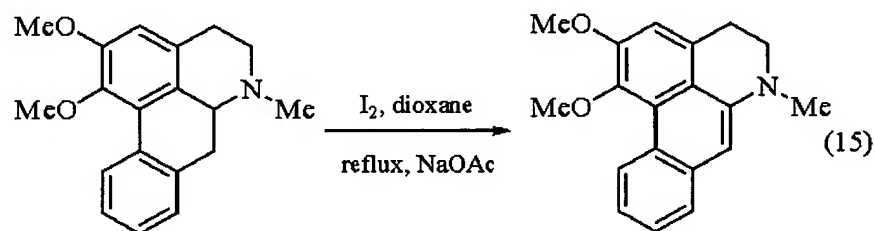
Reactions with Ketones, Aldehydes, and Carboxylic Acid Derivatives.

Iodine reacts with ketones as well as with alkenes. The reaction is usually done in the presence of base and proceeds via the enolate anion. This is the fundamental process that occurs in the Lieben iodoform reaction,[33] in which a methyl ketone reacts with iodine and sodium hydroxide to give iodoform (CHI_3) with oxidative cleavage of the methyl group to produce a carboxylic acid. The H_3C-C bond of methyl carbinols [$RCH(OH)Me$] is also cleaved with this reagent to give the corresponding acid and iodoform. The iodoform reaction constitutes a classical test for the presence of a methyl ketone moiety or a methyl carbinol moiety in an unknown molecule.

Oxidative cleavage is not always the case in this reaction, especially when sodium methoxide is substituted for sodium hydroxide. Steroidal ketones react with iodine and sodium methoxide to give a 58% yield of the α-iodo ketone, when air is excluded from the reaction (eq 18).[6] When oxygen is introduced, an 85% yield of the α,α-diiodo ketone is produced.[6] Reaction of aryl ketones can lead to a different result. 1,2-Diphenyl-1-ethanone reacts with iodine and sodium methoxide at low concentrations to give a 99% yield of 1,2-diphenyl-2-hydroxy-2-ethanone (eq 19).[34] When the concentration of the ketone substrate is increased, the yield of the hydroxy ketone is diminished and a dimer is formed, 1,2,3,4-tetraphenyl-1,4-butanedione (47% yield at 0.2 M).[34]

(18)

0.0071 M	99%	trace	trace
0.2 M	46%	47%	3%

(19)
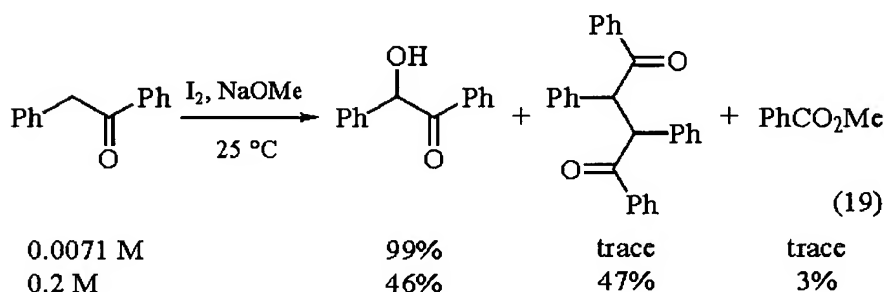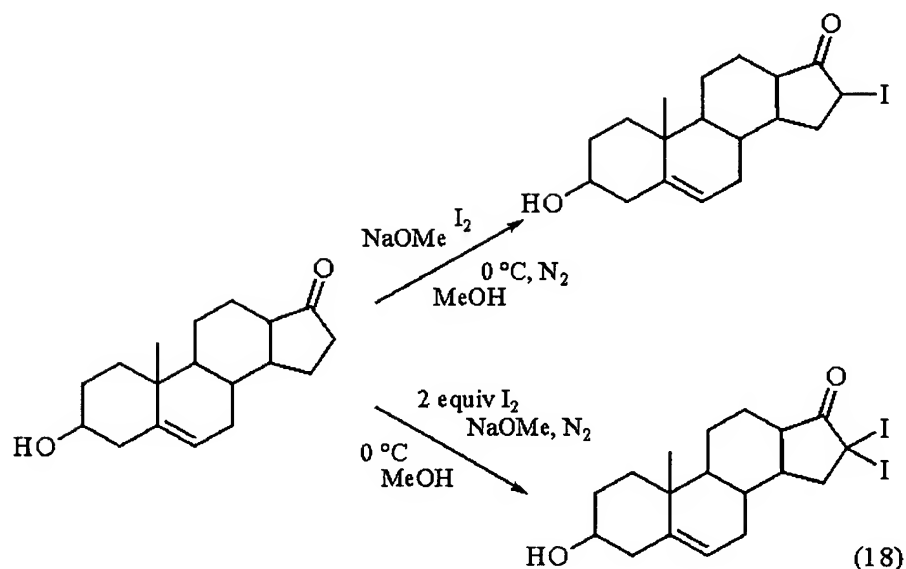
The iodoform reaction clearly shows that iodine behaves as an electrophile in the presence of enolate anions, particularly enolate anions of carboxylic acid derivatives. When 6-heptenoic acid is treated with 2 equiv of **Lithium Diisopropylamide**, and then quenched with iodine, a 70% yield of 2-iodo-6-heptenoic acid is obtained (eq 20).[7] In this particular reaction, 12% of the dicarboxylic acid 2,3-di-4-pentenyl-1,4-butanedioic acid is also obtained, leading to the belief that radical anions are produced in this reaction.[7] Such coupling reactions are also observed with esters which form succinic acid ester derivatives, as in the reaction of ethyl 2-methylpropanoate with 2 equiv of LDA and subsequent reaction with iodine to give an 85% yield of diethyl 2,2,3,3-tetramethyl-1,4-butanedioate (eq 21).[35]

(20)

(21)
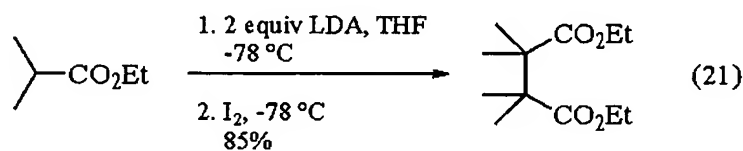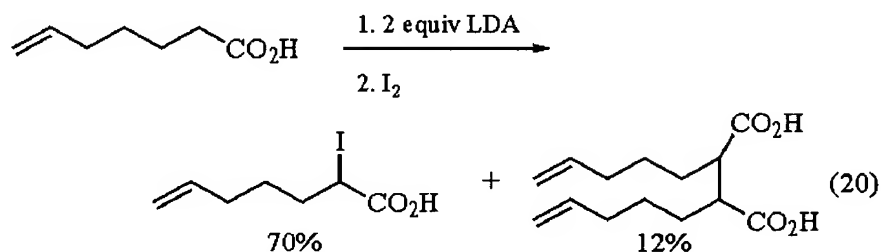
Carboxylic acid derivatives can react with iodine without an intermediary enolate anion to produce α-iodocarboxylic acids. α-Iodocarboxylic acid chlorides can also be produced, as when hexanoic acid

reacts with iodine and ***Thionyl Chloride***, at 85 °C, to give an 80% yield of 2-iodohexanoyl chloride (eq 22).[36] Similarly, butanoic acid reacts with ***Chlorosulfonic Acid*** and iodine to give a 94% yield of 2-iodobutanoic acid (eq 23).[37] These examples are nothing more than the iodine analog of the Hell-Volhard-Zelinsky reaction.[38] The silver salt of pentanoic acid reacts with iodine to produce 1-iodobutane in 67% yiel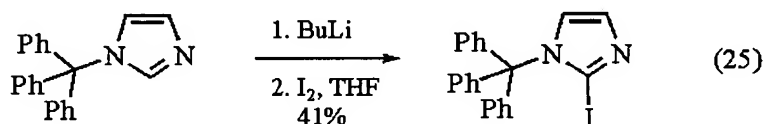d, where decarboxylation occurs under the reaction conditions (eq 24).[39] In general, alkyl iodides are formed from silver carboxylates. This is the iodine version of the Hunsdiecker reaction.[40] Similar reaction occurs when mercury(II) oxide is added, although the yield is lower.

$$
\begin{array}{c}
\text{pentanoic acid} \xrightarrow[\text{2. Na}_2\text{S}_2\text{O}_3]{\substack{\text{1. I}_2,\ \text{SOCl}_2,\ 85\ °\text{C} \\ 90\ \text{min}}} \text{2-iodohexanoyl chloride} \quad (22)
\end{array}
$$

$$
\begin{array}{c}
\text{butanoic acid} \xrightarrow[\substack{\text{ClCH}_2\text{CH}_2\text{Cl},\ 80\ °\text{C} \\ 94\%}]{0.5\ \text{equiv I}_2,\ \text{ClSO}_3\text{H}} \text{2-iodobutanoyl chloride} \quad (23)
\end{array}
$$

$$
\begin{array}{c}
\text{CO}_2^-\ \text{Ag}^+ \xrightarrow[\text{I}_2,\ \text{HgO}\ 36\%]{\text{I}_2\ 67\%} \text{1-iodobutane} \quad (24)
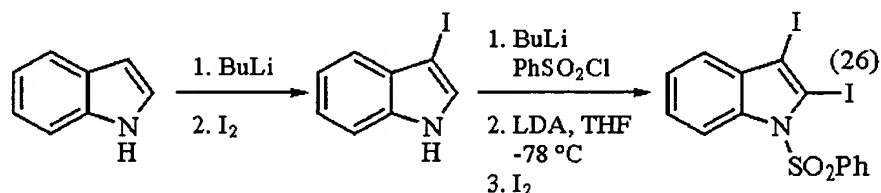\end{array}
$$
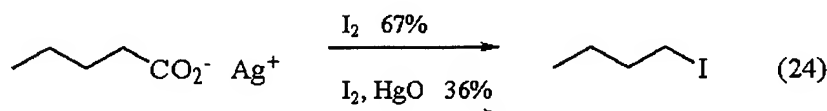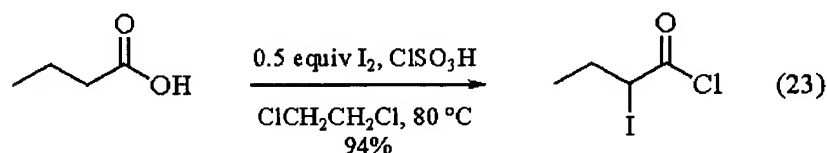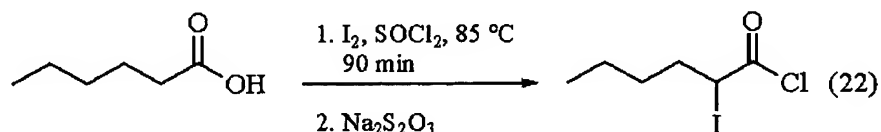
# Iodination of Aromatic and Heteroaromatic Compounds.

Just as enolate anions react with the electrophilic iodine, so also other carbanions react. Iodoimidazoles can be formed, as when *N*-tritylimidazole reacts with ***n-Butyllithium*** and then with iodine, to give a 41% yield of 2-iodo-*N*-tritylimidazole (eq 25).[8]

$$
\text{Ph}_3\text{C-imidazole} \xrightarrow[\substack{2.\ \text{I}_2,\ \text{THF} \\ 41\%}]{1.\ \text{BuLi}} \text{Ph}_3\text{C-2-iodoimidazole} \quad (25)
$$

Iodoindoles can also be produced by this approach. Reaction of indole with *n*-butyllithium and quenching with iodine first produces an *N*-iodoindole, but this is unstable and rearranges under the reaction conditions to 3-iodoindole, in near quantitative yield (eq 26).[41] When this iodo derivative is converted to the *N*-phenylsulfonyl derivative, reaction with LDA and then iodine gives a 98% yield of 2,3-diiodo-*N*-phenylsulfonylindole.[41]

$$
\text{indole} \xrightarrow[2.\ \text{I}_2]{1.\ \text{BuLi}} \text{3-iodoindole} \xrightarrow[\substack{2.\ \text{LDA, THF} \\ -78\ °\text{C} \\ 3.\ \text{I}_2}]{\substack{1.\ \text{BuLi} \\ \text{PhSO}_2\text{Cl}}} \text{2,3-diiodo-}N\text{-phenylsulfonylindole} \quad (26)
$$

Iodopyridine derivatives can also be generated with this technique. 3-Fluoropyridine reacts with LDA and iodine to give a 50% yield of 4-iodo-3-fluoropyridine (eq 27),[42] and 2-chloropyridine reacts with *n*-butyllithium and then iodine to give a 60% yield of 2-chloro-3-iodopyridine (eq 28).[43]

$$\text{(27)}$$

1. LDA, THF, -78 °C

2. I_2

50%

$$\text{(28)}$$

1. t-BuLi, THF, -70 °C

2. I_2, -70 °C

60%
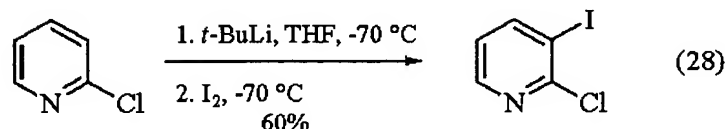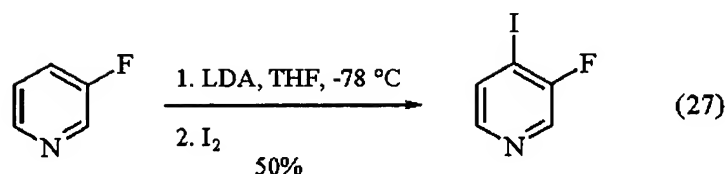
Iodofuran derivatives can be formed, as in the reaction of 2-(dimethyl-t-butylsilyl)furan-3-carboxylic acid with n-butyllithium and iodine, to give a 71% yield of the 4-iodofuran-3-carboxylic acid (eq 29).[44]

1. 2.2 equiv BuLi
-20 °C, 1 h

2. I_2, THF, $MgBr_2$
3. 10% HCl

71%

$$\text{(29)}$$
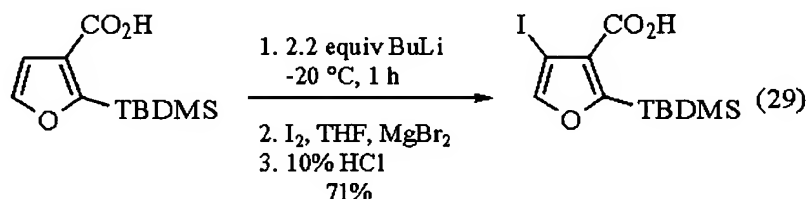
Simple aromatic derivatives can be iodinated to generate iodo-substituted aromatic compounds, if activating substituents are present on the aromatic ring. 1,3-Dicyanobenzene, for example, reacts with LDA and iodine to give a 79% yield of 2-iodo-1,3-dicyanobenzene (eq 30).[45] In general, unactivated aromatics are less useful since formation of the requisite carbanion is somewhat more difficult.

LDA, THF

-96 °C, 3 min

I_2

79%

$$\text{(30)}$$
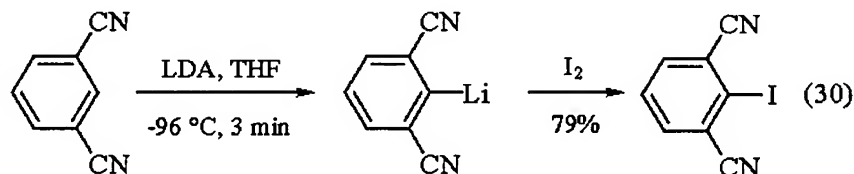
Conversion of Organoboranes to Iodides.

Another important area of chemistry where iodine reactions are important involves organoboranes. When an alkene is reacted with a borane to produce a trialkylborane, subsequent reaction with iodine and sodium hydroxide leads to an iodoalkane. 1-Decene reacts with tri-n-butylborane and then basic iodine to give a 65% yield of 1-iododecane (eq 31).[9]

1. Bu_3B

2. I_2, NaOH

65%

$$\text{(31)}$$
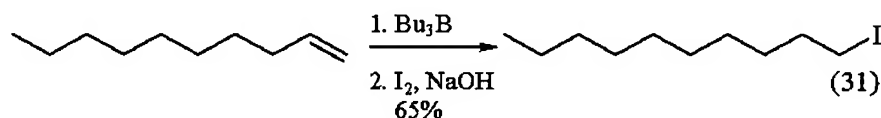
Substituted alkenes can also be prepared from vinylboranes by reaction with iodine and sodium hydroxide. Reaction of dicyclohexylborane with 1-hexyne gives the vinylborane, and subsequent reaction with basic iodine, in THF, gives a 93:7 $cis:trans$ mixture of 1-cyclohexyl-1-hexene in 85% yield (eq 32).[10] When the reaction is done in dichloromethane, a 77:23 $cis:trans$ mixture is produced, but in only 13% yield.[10a] The poor yield is probably due to the poor solubility of iodine in dichloromethane.

(32)

7　　　　:　　　　93
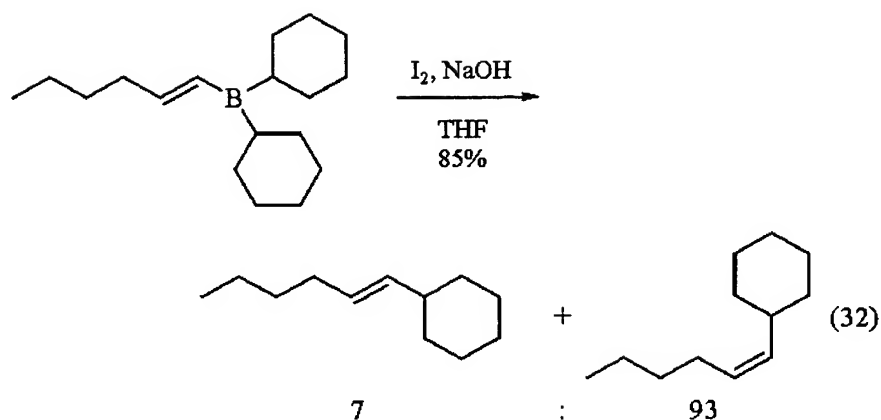
Miscellaneous Reactions.

There are several specialized reactions of iodine that are useful in certain applications. Iodine induces coupling of sodium cyclopentadienide to form 9,10-dihydrofulvalene.[46] Iodine has also been used to cleave iron-carbon bonds in organoiron species.[47] Iodine reacts with hydrazone derivatives to give vinyl iodides.[48]

Reaction with Organic Halides.

An important reaction of iodine is exchange with an alkyl iodide. The most common method for exchanging an iodide is the Finkelstein reaction,[49] which involves treatment of alkyl halides with *Sodium Iodide* to produce alkyl iodides via an S_N2 reaction. Reaction of 1-bromobutane and sodium iodide in dry acetone, for example, gives 1-iodobutane. This exchange also occurs with alkyl iodides. The metal iodides used in this reaction are commercially available, but can be prepared from iodine.

Iodine itself is capable of exchanging the halide atom in alkyl halides, including alkyl iodides, to produce alkyl iodides. The reaction temperatures required are usually greater than 150 °C.[50] Aryl iodides undergo this exchange reaction at even higher temperatures (150-190 °C).[51] α-Iodo ketones also react with iodine, but this occurs at ambient temperatures.[52] The product of these reactions is, of course, another iodide but this is very important in radiolabeling using radioactive iodine isotopes. All of the reactions of iodine involve the use of the natural abundance stable isotope of iodine, ^{127}I. Radiolabeled molecules can be incorporated in a wide range of biological and mechanistic studies. There are at least 10 available isotopes of iodine, but only three are commonly used for labeling: ^{123}I, ^{125}I, and ^{131}I. If these isotopic iodines are used in the preceding reactions, radiolabeled iodides are produced. In the case of the Finkelstein reaction, sodium iodide or *Potassium Iodide* can be produced by synthesizing those salts with radiolabeled iodine. A variety of organic molecules have been radiolabeled for use in biological studies. These include fatty acids,[53] aniline derivatives,[54] quinolines,[55] nucleic acids,[56] steroids,[57] alkyl iodides,[58] aryl iodides,[59] carboxylic acids,[60] and carbohydrates.[61]

Related Reagents.

Dimethyl Sulfoxide-Iodine; Iodine-Aluminum(III) Chloride-Copper(II) Chloride; Iodine-Cerium(IV) Ammonium Nitrate; Iodine-Copper(II) Acetate; Iodine-Copper(I) Chloride-Copper(II) Chloride; Iodine-Copper(II) Chloride; Iodine-Nitrogen Tetroxide; Iodine-Potassium Iodate; Iodine-Silver Acetate;

Iodine-Silver Benzoate; *Iodine-Silver(I) Fluoride*; *Iodine-Silver Trifluoroacetate*; *Lead(IV) Acetate-Iodine*; *Mercury(II) Oxide-Iodine*; *Thallium(I) Acetate-Iodine*; *Triphenylphosphine-Iodine*.

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Iodine-Potassium Iodate

$$\boxed{\textbf{I}_2\textbf{-KIO}_3}$$

(I_2)

[7553-56-2] · I_2 · Iodine-Potassium Iodate · (MW 253.80) (KIO_3)

[7758-05-6] · IKO_3 · Iodine-Potassium Iodate · (MW 214.00)

(conversion of alkenes to iodohydrins;[1] iodination of some aromatic molecules;[2] the iodohydrins (or iodoacetates) formed are readily converted to *cis*-diols[3])

Physical Data: KIO_3: mp 560 °C; *d* 3.930 g cm^{-3}. I_2: see ***Iodine***.

Solubility: KIO_3: sol water: 9.16 g/100 g water at 25 °C and 32.2 g/100 g water at 100 °C.[4] In other work, the solubility in water was measured to be: 8.40 g KIO_3/100 g water at 25 °C; 13.7 g/100 g at 50 °C; and 24.4 g/100 g at 100 °C.[5] It shows some solubility in aqueous dioxane mixtures: 8.472 g/100 g (0% dioxane:100% water); 5.30 g/100 g (10% dioxane); 3.172 g/100 g (20% dioxane); 1.811 g/100 g (30% dioxane); 0.886 g/100 g (40% dioxane); and 0.471 g/100 g (50% dioxane). KIO_3 insol pure dioxane and most common organic solvents.

Form Supplied in: the active reagent is generated in situ, as needed. KIO_3: colorless monoclinic crystals; commercially available in at least 99.5% purity.

Preparative Method: in reactions with alkenes, the following ratio of reactants is typical: alkene:KIO_3:I_2, 4:1:2 in acetic acid.[3] The iodine and potassium iodate are premixed in acetic acid at ambient temperatures and then treated with the organic substrate and allowed to react at a suitable temperature.

Handling, Storage, and Precautions: the reagent should be prepared in solution, as needed, and used in situ. Potassium iodate is an irritant, particularly of the upper respiratory tract. Ingestion causes headache, nausea and vomiting, dizziness, and gastrointestinal irritation. Avoid ingestion, skin contact, and eye contact. Potassium iodate is a powerful oxidant and should not be stored near combustible materials, near flammable materials, or near powdered metals. Mixing with powdered metals can cause an explosion. It should be stored in a separate and tightly closed container. This combination reagent should be handled in a fume hood.

Addition to Alkenes.

Potassium iodate is a powerful oxidant and *Iodine* is an electrophilic reagent. When mixed together in acid media, the combined reagent converts alkenes to iodohydrins, which can be converted to *cis*-diols. Cornforth reacted propene with a mixture of iodine and potassium iodate, in aqueous sulfuric acid, and obtained a 92% yield of 1-iodo-2-propanol, along with 8% of 2-iodo-1-propanol (eq 1).[1] When the same reaction is done in acetic acid and aqueous dioxane, a 78% yield of the iodohydrin is obtained.
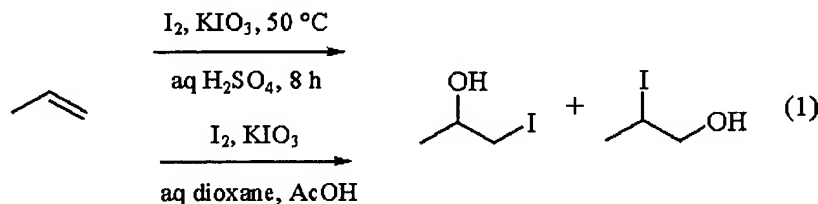
This fundamental iodohydrin procedure has been modified to produced *syn*-diols from alkenes. When cyclohexene is treated with I_2/KIO_3 in acetic acid, the *trans*-iodohydrin is formed. Subsequent reflux of this product with aqueous acetic acid or with aqueous DMSO produces *syn*-1,2-cyclohexanediol in 70% yield.[1] This same procedure has been applied to 5α-cholest-2-ene to give 2β-acetoxy-3α-iodo-5α-cholestene (eq 2). Refluxing in aqueous acetic acid leads to an 84% yield of 5α-cholestene-2β,3β-diol.[1,6] This two-step procedure is a useful alternative to the Woodward-Prévost reaction (see *Iodine-Silver Acetate*) that produces *syn*-diols from alkenes. This I_2/KIO_3 procedure is attractive for this purpose since it does not rely on expensive silver reagents.
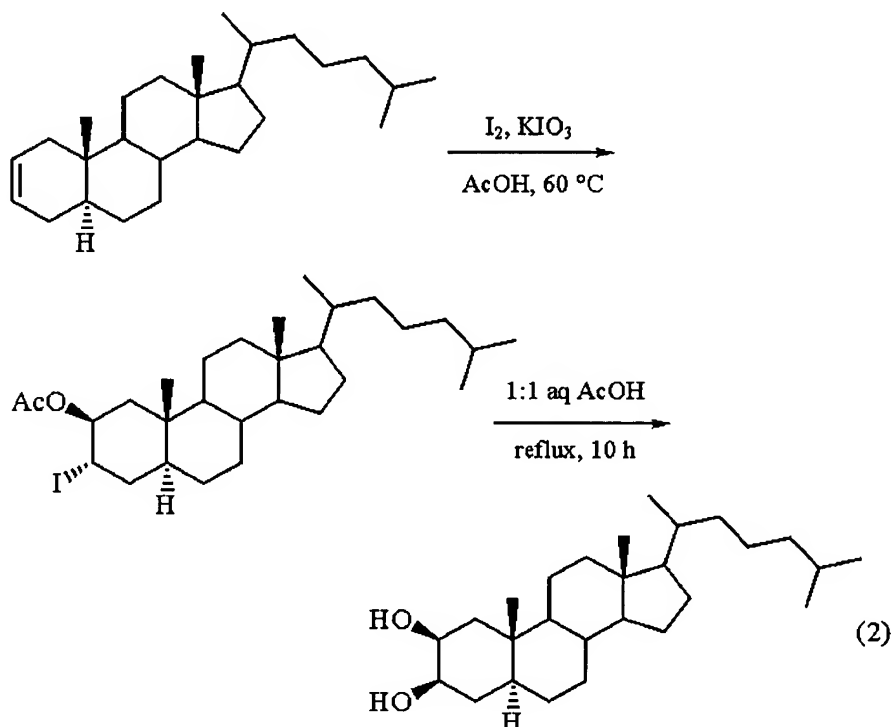
Quinones can be converted to iodoquinones with this mixed reagent. When 2-dimethylamino-1,4-benzoquinone is treated with iodine/potassium iodate in a solvent of ether and aqueous sulfuric acid, 2-dimethylamino-3-iodo-1,4-benzoquinone is formed, but in only 22% yield (eq 3).[3]

(3)
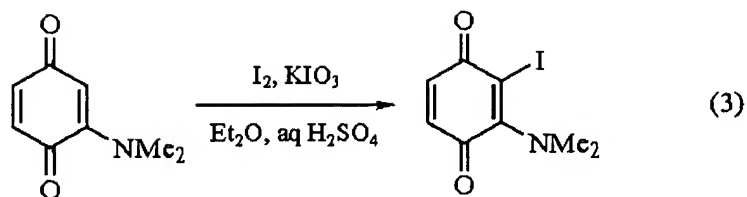
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